UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,170	07/20/2007	Gen-Sheng Feng	BURNHAM.010NP	7231

20995 7590 06/24/2011

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
06/24/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
efiling@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,170	FENG ET AL.	
	Examiner	Art Unit	
	VALARIE BERTOGLIO	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28-31 and 44-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,28-31 and 44-52* is/are rejected.

7)☐ Claim(s) *53-59* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/16/2010 has been entered.

Claims 1-25,27,32-43 are cancelled. Claims 53-59 are added.

Claim Objections

Claim 53 (and dependent claims 54-59) is objected to because of the following informalities: the preamble of the claim recites that the mouse 'comprises' an increased body weight. Body weight is a characteristic that is 'exhibited' by a mouse, not 'comprised' by a mouse. Furthermore, this limitation is actively recited in the body of the claim and need not be recited in the preamble. Appropriate correction is required.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28-31 and 44-52 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a genetically modified mouse whose genome comprises a $Shp2^{flox}$ allele wherein the Shp2 gene is functionally disrupted in CamK2a-expressing cells such that no Shp2 is expressed in said cells and wherein said mouse exhibits increased body weight, early-onset obesity, and

resistance to leptin, does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is maintained for reasons set forth in the office action dated 08/19/2010 and reiterated in the office action dated 02/15/2011.

The claims are directed to genetically modified mouse comprising a disrupted Shp2 gene wherein said mouse is homozygous for said disrupted gene and exhibits increased body weight in comparison to a wildtype control mouse. Dependent claims recite additional phenotypes. The claims encompass mice that have a disruption in the Shp2 gene in all cells of the mouse or in cells other than cells of the forebrain.

The specification teaches a conditional knockout of the Shp2 gene in CamK2a-expressing forebrain cells (CaSKO mouse). The specification teaches use of a homologous recombination construct with loxP sites flanking exon 4 of the Shp2 gene to generate a line of mice ($Shp2^{flox}$) that, when crossed to a Cre-expressing line, will lose expression of Shp2 in Cre-expressing cells. Cre-mediated recombination results in deletion of exon4 and a frameshift that results to premature truncation. The specification teaches crossing the $Shp2^{flox}$ mouse to a mouse where the promoter driving expression of a Cre recombinase transgene is the CaMK2a promoter. The CaMK2a promoter drives expression *only in the neurons of the hippocampus* (see Reece 2004, page 388, provided herewith). The pattern of expression of the Cre recombinase determines which cell will lose expression of Shp2, which will then determine the phenotype of the mouse. The specification has taught only the CaSKO mouse lacking Shp2 in CaMK2a expressing cells. The specification has not taught other mice encompassed by the claims.

The art has demonstrated other conditional knockouts of the Shp2 gene wherein loss of Shp2 expression from other cells types, resulting from use of different promoters driving Cre expression, leads to phenotypes other than those claimed and disclosed in the specification (for example, see Grossman, PNAS. 2009, 106:16704-16709; Nakamura, PNAS, 2009, 106:11270-11275). The art has also

demonstrated that a non-conditional knockout of Shp2 in all cells of a mouse is embryonic lethal (Saxton, 1997, EMBO J, 16:2352-2364). Therefore, the specification enables making only a mouse lacking Shp2 expression in CaMK2a-expressing cells with the claimed phenotypes. The phenotypes of other Shp2-disrupted mice would differ from those of the mice disclosed in the specification for the CaSKO mouse and therefore, the specification fails to enable those other mice encompassed by the claims.

Therefore, because the specification only teaches use of the CaMK2a promoter to drive Cre-mediated recombination to knockout the Shp2 gene in forebrain cells to obtain a mouse with the claimed phenotypes, and because loss of Shp2 activity in other cells results in other phenotypes, including lethality, the specification fails to enable any mouse other than a genetically modified mouse whose genome comprises a $Shp2^{flox}$ allele wherein the Shp2 gene is functionally disrupted in CamK2a-expressing cells such that no Shp2 is expressed in said cells and wherein said mouse exhibits increased body weight, early-onset obesity, and resistance to leptin.

Applicant argues the specification need only disclose one method for making and using the claimed invention. In response, the specification fails to teach making the mice encompassed by the claims. The mice of the rejected claims are not limited to the mouse taught in the specification. Applicant argues that other promoters are known that could be used in the claims. This argument is not persuasive because use of other promoters would express in a different subset of cells of the forebrain and the effect of such an expression pattern is unpredictable for reasons previously made of record. As previously set forth, it would not be predictable that the claimed phenotypes would be obtained when using other forebrain-specific promoter that express in a different subset of forebrain cells as well as different cells outside the forebrain.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to VALARIE BERTOGLIO whose telephone number is (571)272-0725. The examiner can normally be reached on Mon-Fri 6:30-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner, Art Unit 1632